

QT interval and dispersion in primary autonomic failure

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Abstract

Objective—To investigate the role of the autonomic nervous system in determining QT interval and dispersion.

Patients and methods—32 patients with chronic primary (idiopathic) autonomic failure (19 men, mean age 60 years) and 21 normal controls (11 men, mean age 59) without symptoms of ischaemic heart disease were studied retrospectively. Autonomic failure was diagnosed by a combination of symptomatic postural hypotension, subnormal plasma norepinephrine response to head-up tilt, and abnormal cardiovascular responses to standing, Valsalva manoeuvre, mental stress, cutaneous cold, isometric exercise, and deep breathing. QT intervals were measured from surface electrocardiograms and QT dispersion was defined as maximum QT – minimum QT occurring in any of the 12 leads.

Results—Mean heart rate (RR intervals) was similar in patients with autonomic failure and controls (S2 lead: 865 (132) v 857 (108) ms, $P = \text{NS}$; V2 lead: 865 (130) v 868 (113) ms, $P = \text{NS}$). QT intervals measured from electrocardiogram leads S2 and V2 were significantly longer in patients than in controls (401 (40) v 376 (16) ms, $P < 0.01$; and 403 (41) v 381 (20) ms, $P < 0.05$ respectively). The mean maximum QT interval in any lead, which is the best estimate of the maximum duration of electrical systole, was significantly longer in the patients than in controls (417 (48) v 388 (23) ms, $P < 0.005$). Linear regression analysis of QT and RR intervals for both groups showed a significant difference between the slopes of the two regression lines ($F = 8.4$, $P < 0.001$). However, QT dispersions were similar between patients and controls.

Conclusions—Patients with primary autonomic failure have prolongation of QT intervals, indicating that the autonomic nervous system is an important determinant of QT interval. However, QT dispersion does not seem to be affected by chronic primary autonomic denervation.

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Keywords: QT interval and dispersion; primary autonomic failure; electrocardiography; autonomic nervous system

The QT interval is the electrocardiographic description of ventricular depolarisation and repolarisation, which when abnormal may identify patients at risk of developing ventricular fibrillation and sudden cardiac death.^{1,2} The autonomic nervous system is believed to be an important element in the genesis of malignant ventricular arrhythmias and sudden death.³ Changes in the autonomic neural tone may affect the QT interval by affecting depolarisation and repolarisation kinetics of myocardial cells through neural or receptor mediated mechanisms, or both.^{4,5} There is increasingly convincing evidence that dispersion of ventricular refractoriness is associated with ventricular instability and ventricular arrhythmias.^{6,7} Dispersion of the QT interval on the surface electrocardiogram may provide a non-invasive measure of dispersion of repolarisation.^{8,9} The influence of the autonomic nervous system on the QT interval is currently incompletely understood, partly because previous studies have investigated patients with secondary autonomic neuropathy in whom the primary disorder may have also affected the cardiovascular system. The most commonly studied group of patients are diabetics with autonomic neuropathy,¹⁰⁻¹² in whom diabetic cardiomyopathy may occur and coronary artery disease is common. Normal individuals in whom pharmacological agents have been administered to block partially, or completely, the adrenergic receptors to mimic autonomic failure have also been studied.^{6,13} To overcome these difficulties and gain further insight into the role of the autonomic nervous system, a unique group of patients with chronic primary autonomic failure, who had no cardiac disease and were a physiological model of autonomic denervation, was studied, with the specific aims of evaluating the effects of autonomic failure on QT interval and dispersion.

Patients and methods

STUDY POPULATION

Patients with chronic primary autonomic failure from the Autonomic Unit, National Hospital for Nervous Diseases and the Neurovascular Medicine Unit, St Mary's Hospital, London were studied. None had evidence of diabetes mellitus, chronic liver disease, or amyloidosis. Apart from autonomic failure, they had either no neurological deficit (pure autonomic failure), or additional parkinsonian, cerebellar/pyramidal, or a combination of these neurological deficits, as part of the

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syndrome of Shy-Drager (often used synonymously with multiple system atrophy).¹⁴ The study population consisted of patients who had a 12 lead electrocardiogram recorded at the time that autonomic failure was diagnosed by a series of physiological and biochemical tests.¹⁵ All patients had severe symptomatic postural hypotension (> 30 mm Hg decrease in systolic blood pressure). Sympathetic failure was indicated by the combination of a lack of pressor response to cutaneous cold, isometric exercise and mental arithmetic, an abnormal Valsalva response, and an absent or minimal response in plasma noradrenaline levels to head-up tilt. In addition, all patients had either blunted or no heart rate response to deep breathing and hyperventilation, indicating cardiac parasympathetic failure. Patients were excluded if they had any of the following: (1) history of cardiac ischaemia, (2) history of alcohol abuse, (3) arrhythmia, bundle branch block pattern or significant Q waves on electrocardiogram, (4) serum creatinine of > 150 $\mu\text{mol/l}$, (5) biochemical evidence of chronic liver disease as judged by serum albumin < 30 g/l, (6) medication known to affect QT interval, (7) diabetes, and (8) a family history of sudden death. Seventeen patients with pure autonomic failure and 15 patients with Shy-Drager syndrome were selected for the study. They were compared with a group of normal individuals of similar age and sex, recruited from the local community. The mean age of the 21 controls (11 men) was 59 years and that of the 32 patients with chronic primary autonomic failure (19 men) 60 years at the time that autonomic failure was diagnosed.

QT MEASUREMENT AND ANALYSIS

QT intervals were measured in a blinded fashion from routine standard 12 lead electrocardiograms recorded at 25 mm/s at rest. The QT and RR intervals of at least one sinus beat (range 1–3) were measured from each of the 12 leads, and the mean QT and RR intervals calculated. In addition, QT and RR intervals of at least five consecutive sinus beats (range 5–7) were measured from lead S2, which was the rhythm strip on the same electrocardiographic tracings. The QT and RR intervals were measured manually with calipers. QT intervals were measured from the onset of the QRS complex to the end of the T wave. The end of the T wave was defined as the point of return to the isoelectric line (i.e. regardless of the polarity of the T wave).¹⁶ For inclusion in the study, the T wave had to be distinct with a clearly defined termination. Biphasic T waves were measured to the time of final return to baseline. QT intervals were not measured in leads when U waves were present, which were not frequently encountered in our patients. Electrocardiographic leads S2 and V2 were used for QT interval analysis. QT dispersion was defined as the difference between the maximum and minimum QT intervals occurring in any of the 12 leads. All measurements were performed by a single observer. Repeatability of the QT measurements was tested by a second observer, who measured

the same QT intervals of lead S2 in 16 randomly selected electrocardiograms.

ELECTROLYTE STUDIES

Plasma potassium and calcium concentrations were measured at the same time as when the electrocardiograms were recorded.

STATISTICAL ANALYSIS

Data are presented as means (SD), and the 95% confidence intervals (CI) for the differences between the means have been calculated. Student's *t* test was used for unpaired data. Logarithmic transformation was carried out for skewed data. Analysis of variance was applied to the regression slopes between QT and RR intervals. Differences were considered to be significant when $P < 0.05$.

Results

Plasma potassium (4.1 (0.4) (range 3.2–5.7) mmol/l) and corrected calcium (2.31 (0.11) (range 2.10–2.52) mmol/l) concentrations in the patients were normal at the time of the study.

QT INTERVAL

Table 1 shows the RR and QT intervals measured from leads S2 and V2. The RR intervals were similar between the patients and controls. QT intervals were significantly longer in the patients than in controls (table 1). The 95% CI for the difference between the means for lead S2–QT were 6.0–41.9 ms ($P < 0.01$) and for lead V2–QT 10.0–46.0 ms ($P < 0.05$). However, QT dispersions were similar between patients and controls (42.0 (16.8) *v* 38.6 (14.4) ms, $P = \text{NS}$). The number of leads in which QT intervals were measured was similar in the two groups (range 9–12). The mean of the maximum QT interval in any lead, which is the best estimate of the maximum duration of electrical systole, was significantly longer in the patients than in controls (417 (48) *v* 388 (23) ms, $P < 0.005$) (table 2).

In the 16 randomly selected electrocardiograms (six controls), QT intervals measured

Table 1 Results of RR and QT intervals

	Controls (<i>n</i> = 21)	Patients (<i>n</i> = 32)
Lead S2		
RR interval (ms)	857 (108)	865 (132)
QT interval (ms)	376 (16)	401 (40)†
Lead V2		
RR interval (ms)	868 (113)	865 (130)
QT interval (ms)	381 (20)	403 (41)*

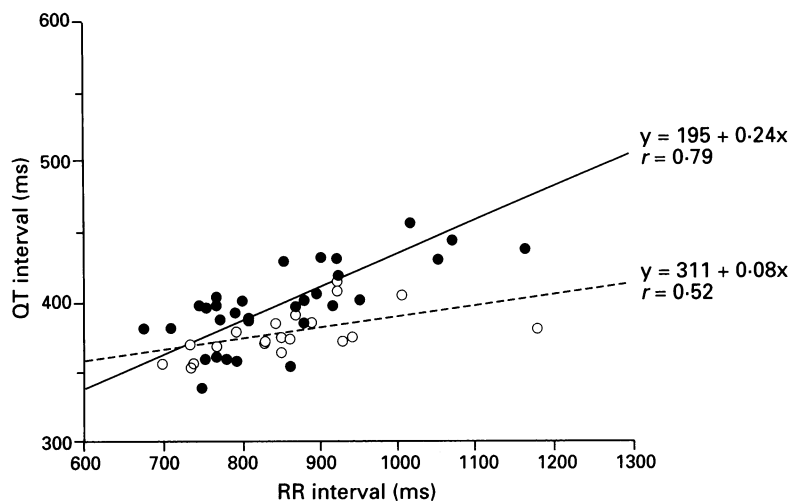
Results are expressed as mean (SD).

* $P < 0.05$; † $P < 0.01$.

Table 2 Maximum QT intervals

	Controls (<i>n</i> = 21)	Patients (<i>n</i> = 32)
QT max (ms)		
Mean	388 (23)	417 (48)*
Range	344–420	368–584
Median	380	410

* $P < 0.005$ *v* controls.



Relation between QT and RR intervals derived from electrocardiogram lead S2. Patients are represented by the closed circles and continuous line, and controls by the open circles and interrupted line.

from lead S2 were similar between observer one and observer two (377 (16) *v* 378 (25) ms, 95% CI -0.73 to 7.36; *P* = 0.3 and *r* = 0.95).

RELATION BETWEEN QT AND RR INTERVALS

The figure shows the relation between QT and RR intervals from lead S2. Linear regression analysis of the distribution of QT and RR values in both groups was described by the regression equation $y = a + bx$. The regression coefficient for the patients ($a = 195$, $b = 0.24$, $r = 0.79$) was significantly different from that of the controls ($a = 311$, $b = 0.08$, $r = 0.52$) ($P < 0.001$). The difference between the slope of the patients and that of the controls was highly significant ($F = 8.4$, $P < 0.001$).

Discussion

The results of this study show a clear and significant difference in mean and maximum QT intervals between patients with primary autonomic failure and normal controls. Previous studies have shown the important influence of the autonomic nervous system on QT interval in diabetic patients with autonomic neuropathy and cardiac transplant recipients with anatomically denervated hearts,¹⁰⁻¹² and by using pharmacological agents that block either limb of the autonomic nervous system.^{6,13} Some of our patients with documented primary autonomic failure had normal QT intervals, indicating that at the time of measurement, there was a balanced dysfunction of the sympathetic and parasympathetic nervous systems, or that the autonomic nervous system was not the only determinant of QT interval.

There is no consensus regarding the optimal lead for QT interval measurement. The reliability of QT interval measurement depends on the accuracy and precision in determining the earliest onset of the QRS complex and the end of the T wave. The onset of the initial QRS deflection is frequently not simultaneous in all leads. It has been reported that the right precordial leads (V1 and V2) are the most reliable

and the onset of QRS is never delayed, and that the QT interval can be reliably assessed by simultaneously recording a right precordial lead and a limb lead.^{16,17} We selected lead S2 as our limb lead and lead V2 as the right precordial lead.

Our study consisted of patients who when diagnosed were not taking medications that affected QT intervals. None of our patients had familial prolongation of the QT interval associated with sinus bradycardia, recurrent syncope, and sudden death from ventricular arrhythmias.¹ Although we were not able to measure QT intervals in the first degree relatives of our patients, none had a family history of sudden death. Abnormalities of the QT interval have been reported in several different patient populations, including patients with diabetes,^{10,11,18} myocardial ischaemia and dysfunction,^{2,18,19} alcoholism and chronic liver disease,^{20,21} and severe hypocalcaemia or hypokalaemia.²² In our study, however, patients with symptoms or electrocardiographic evidence of myocardial ischaemia and a history of alcoholic abuse were excluded, and biochemical analysis of blood glucose, serum albumin, plasma calcium and potassium were all within normal limits. Primary autonomic neuropathy was therefore the most likely cause of the QT interval prolongation in this study.

The two limbs of the autonomic nervous system provide a normal synergistic interaction such that alteration of this balance may result in changes in QT intervals. Most human and animal studies have shown that the sympathetic system exerts a shortening effect on refractory periods and QT duration, while the parasympathetic system prolongs both these variables.^{5,6,12} A sympathetic imbalance between the right and left stellate ganglia has been found in the hereditary long QT syndrome. Left cardiac sympathetic denervation was related to an improvement in frequency of syncopal attacks and patient survival.²³ However, QT interval normalisation only occurred in 11.5% of the patients, suggesting that other mechanisms are involved in determining QT intervals.²³ One such mechanism may be an intracardiac abnormality possibly related to potassium conductance.²⁴ The precise mechanism causing QT interval prolongation in our patients is not clear. Sympathetic dysfunction is possibly more significant than parasympathetic dysfunction in patients with primary autonomic dysfunction, or it may be that both limbs are affected equally but the sympathetic system exerts a greater influence on the normal QT interval than the parasympathetic system.

QT interval prolongation may reflect an increased dispersion of ventricular repolarisation time and may provide a mechanism of arrhythmogenesis that involves the triggering of arrhythmias by critically timed ventricular extrasystoles.⁷⁻⁹ However, the normal QT dispersion in the patients indicated that the QT prolongation in primary autonomic failure is not associated with increased temporal dispersion of ventricular recovery time, but reflects a global increase in ventricular recovery time.

The abnormal QT dispersion that is well documented in patients with coronary artery disease may be linked to ischaemic related heterogeneity of repolarisation or imbalance in sympathetic activity due to regional cardiac autonomic denervation, or alterations in calcium flux.²⁻²⁵ Certainly, the critical component is myocardial necrosis and injury, creating a dispersion of myocardial refractoriness that in conjunction with heightened sympathetic tone creates electrical instability and cardiac arrhythmias.²⁵

This unique group of patients with primary autonomic failure provided further insights to the important influence of autonomic tone on QT interval and dispersion. Primary autonomic failure was associated with QT interval prolongation but did not increase temporal dispersion of ventricular recovery time. Autonomic neuropathy may have important prognostic implications in these patients. Some 56% of diabetic patients with autonomic neuropathy die within five years of diagnosis.²⁶ In patients with chronic liver disease the cumulative four year mortality rate was 30% in those with autonomic neuropathy, compared with 6% in those without autonomic neuropathy.²⁷ The six year survival rate after primary autonomic failure related to multiple system atrophy was diagnosed was 54%.²⁸ The exact explanation for the increased death rate is unknown but sudden death due to sleep apnoea and cardiorespiratory arrest was reported in many cases.²⁶⁻²⁸ We have not assessed the complex interrelation between QT interval, ventricular arrhythmias, and sudden death, although the presence of QT interval prolongation in these patients may increase their vulnerability to arrhythmia.

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